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Year: 2018

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## **Urticaria and Angioedema: an Update on Classification and Pathogenesis**

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DOI: <https://doi.org/10.1007/s12016-017-8628-1>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-139444>

Journal Article

Accepted Version

Originally published at:

Radonjic-Hoesli, Susanne; Hofmeier, Kathrin Scherer; Micaletto, Sara; Schmid-Grendelmeier, Peter;  
Bircher, Andreas; Simon, Dagmar (2018). Urticaria and Angioedema: an Update on Classification and  
Pathogenesis. *Clinical Reviews in Allergy Immunology*, 54(1):88-101.

DOI: <https://doi.org/10.1007/s12016-017-8628-1>

# Urticaria and Angioedema: an Update on Classification and Pathogenesis

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# Springer Science+Business Media, LLC 2017

Published online: 26 July 2017

**Abstract** Urticaria is a common, mast cell-driven disease presenting with wheals or angioedema or both. In the last years, urticaria has increasingly attracted notice to clinicians and researchers, last but not least inspired by the approval of omalizumab, an anti-IgE antibody, for urticaria treatment. There is wide consensus on the clinical classification based on duration and elicitation. However, the pathogenesis is incompletely understood. This review summarizes current guidelines for the management and novel insights in the pathogenesis of urticaria with special focus on their impact on clinical praxis. The classification of urticaria subgroups is mainly based on clinical criteria: acute and chronic urticaria (CU). Chronic urticaria comprises both chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU) that includes physical and non-physical urticarias. Recent research focused on characterizing the role of cells and mediators involved in the pathogenesis of urticaria, identifying the mechanisms of mast cell activation, and investigating underlying autoimmune processes in chronic spontaneous urticarial. Currently, non-sedating antihistamines and omalizumab, an antiimmunoglobulin E antibody, are recommended for the therapy of chronic urticaria, as both exhibit a favorable

efficacy and safety profile. Novel therapeutic strategies aim at specifically targeting cells and mediators involved in the pathogenesis of urticaria.

**Keywords** Angioedema . Mastcell . Histamine . Omalizumab . Urticaria

## Abbreviations

ACE	Angiotensin converting enzyme
ACU	Acquired cold urticaria
AE	Angioedema
AIU	Autoimmune urticaria
ASST	Autologous serum skin test
ChU	Cholinergic urticaria
CIndU	Chronic inducible urticaria
CRTH2	Chemoattractant receptor-homologous molecule expressed on TH2 cells
CU	Chronic urticaria
CSU	Chronic spontaneous urticaria
DPU	Delayed pressure urticaria
Ig	Immunoglobuline
IL	Interleukin
PG	Prostaglandin
SU	Solar urticaria
TNF	Tumor necrosis factor

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TPO      Thyperoxidase  
UAS      Urticaria activity score

Urticaria is a common disease as in acute form affects 20% of the general population and chronic urticaria (CU) up to 5% [1]. Recent progress in the therapy of chronic urticaria with the approval of omalizumab has extensively stimulated clinical and basic research in the field. In this review, we highlight novel insights in the pathogenesis and management of urticaria which we selected because of their potential impact on daily practice.

## Current Definitions

Urticaria is defined as the sudden development of transient hives (wheals) and angioedema or both [2]. A wheal is characterized by a circumscribed superficial edema of the skin, mostly surrounded by a bright red erythema and associated with a strong itching or burning sensation. In urticaria, wheals develop within several minutes and have a transient nature inasmuch as the skin returns to its normal appearance within 1–24 h. Angioedema presents as painful or burning, non-itchy, and less well-demarcated edema of the deep dermis and subcutis, or mucous membranes. Usually, angioedema appears as skin-colored or slightly red swellings and, compared to wheals, they slowly develop and may persist for several days [2]. In addition to the skin and adjacent mucosa, the gut is typically affected by certain types of angioedema, e.g., hereditary angioedema. Angioedema of the pharynx or larynx may be life threatening through the risk of asphyxiation [3].

## Clinical Classification of Urticaria

Current classifications consider both duration and causes/triggers of urticaria [2, 4]. Acute urticaria is defined by a repeated appearance of wheals with or without angioedema over a period of up to 6 weeks, whereas the recurrence of lesions over more than 6 weeks is considered as chronic [2]. In 10–20% of the cases, angioedema may be the first and often only manifestation of urticaria. Approximately 60% of the patients with chronic spontaneous urticaria (CSU) report on angioedema episodes [5]. For a comprehensive review on the differential diagnosis of angioedema without urticaria, see a very recent review in this journal [3].

A recent study reported a high frequency of systemic signs and symptoms such as joint pain or swelling (55.3%), headache/fatigue (47.6%), flushing (42.7%), wheezing or breathlessness (30.1%), gastrointestinal complaints (26.2%), and palpitations (9.7%) in two thirds of adult patients with CSU that are probably under-recognized in

daily practice [6]. Interestingly, the number of organs involved did not correlate with serum tryptase levels [6].

Depending on whether the skin lesions appear spontaneously or can be induced by a specific trigger, urticaria is classified as either CSU or chronic inducible urticaria (CIndUs) [2, 4]. Within the group of CIndUs, symptomatic dermographism/urticaria factitia, cold- and heat-induced urticarias, delayed pressure urticaria, solar urticaria, and vibratory angioedema are defined as physical urticarias. Non-physical CIndUs include cholinergic urticaria, contact urticaria, and aquagenic urticaria [4].

## Chronic Spontaneous Urticaria

A nationwide epidemiological study revealed an annual prevalence of CSU ranging from 0.02% in 2002 to 0.38% in 2013 and an incidence of 0.10–1.50 per 1000 person-years in Italy [7]. For both prevalence and incidence rates, female patients outnumbered males: 0.48 versus 0.23% and 1.6 versus 0.8 per 1000 person-years, respectively [7]. Obesity, anxiety, dissociative and somatoform disorders, and malignancies were associated with an increased risk to develop CSU [7]. Among patients with CSU, two thirds reacted to physical triggers [8]. CSU is considered a mast cell-driven disease triggered by infections, food or drug intolerance, activation of the coagulation cascade, genetic disposition, or autoimmunity [9]. Both type I (IgE mediated) and type II (autoantibodies of IgG or IgM type) hypersensitivity reactions have been associated with CSU [9]. The autologous serum skin test (ASST: intradermal injection of patients own serum) is often used as screening for autoimmune CSU since some studies found positive reactions more frequently in CSU patients compared with healthy controls, atopic individuals, or CIndUs [9]. In order to test the presence and functional activity of anti-IgE and anti-IgE receptor autoantibodies, additional diagnostic tests with ELISA or Western blot and basophil activation test have been recommended [10].

## Chronic Inducible Urticarias

### Symptomatic Dermographism

Urticarial dermographism is the most frequent form of physical urticaria with an estimated prevalence of 5% of the general population [11]. Symptomatic dermographism is an exaggerated response to a relatively minor stroking pressure, rubbing, or scratching, e.g., induced by trouser waistbands, cuffs, or collars [12]. Usually, the wheals disappear within minutes after cessation of the causative stimulus. Recently, an instrument for assessing provocation

threshold levels in patients with symptomatic dermatographism has been developed (Fig. 1) [13].

### Acquired Cold Urticaria

Acquired cold urticaria (ACU), the second most frequent type of physical urticaria, is characterized by lesions developing upon exposure to cold air, liquids, or solids and occurs more frequently in women than men [4, 14].

Fig. 1 Urticarial dermatographism induced by a dermatographometer on the back of patient (left) and a wheal provoked by cold exposure in a patient with acquired cold urticaria (4 °C, right)



Extensive cold contact, e.g., diving in cold water, may provoke systemic symptoms such as dyspnea, hypotension, and loss of consciousness in addition to wheals resembling anaphylaxis and may lead to death [15]. A retrospective study revealed a mean temperature threshold of  $13.7 \pm 6.0$  °C; range 26–4 °C (Fig. 1) [14]. Siebenhaar et al. subclassified primary and secondary ACU, without or with underlying cause, respectively [16]. ACU has been associated with viral, bacterial, and parasitic infections as well as cryoglobulinemia with monoclonal IgG or mixed types of IgG/IgM and IgG/IgA [16]. There are case reports on ACU associated with hymenoptera stings, food and drug intolerance, low C1-inhibitor and C4 as well as altered chemokine levels [16]. Atypical variants of ACU are summarized in Table 1 [16, 17].

### Heat-Induced Urticaria

In heat urticaria, a very rare variant of physical urticaria, a circumscribed wheal and flare reaction develops immediately after local heat exposure to the skin. Atypical familial as well as pediatric cases have been published. The wheals usually persist for 1–3 h [18].

### Delayed Pressure Urticaria

Delayed pressure urticaria (DPU) presents with angioedemalike swellings at areas of the skin and mucosa exposed to pressure. Classical wheals do not occur in DPU.

Painful swellings, itching, or burning occur several hours after exposure to vertical pressure and may persist for hours, sometimes longer than 24 h. Triggers are carrying backpacks or bags with shoulder straps, sitting on hard chairs, tight shoes, carrying heavy bags by hand. DPU often coexists with CSU or other types of physical urticaria. DPU should be distinguished from symptomatic dermatographism in which friction induces wheals without delay and of short duration, e.g., lesions under the belt or

bra [18].

### Solar Urticaria

In most patients with solar urticaria (SU), the trigger is a UV-A light, while provocation by visible or UV-B light is less frequent. SU is rare: 0.08% among urticaria patients, 2.3% of the patients with acute sun-induced skin problems. Female predominance, an association with atopy but not with skin pigmentation type as well as concomitant other types of CU have been reported in SU [19]. Upon activation by light, serum or dermal factors, that have not been further specified, have been assumed to cause mast cell degranulation [20]. Omalizumab may be helpful in some SU patients [21, 22].

### Cholinergic Urticaria

Cholinergic urticaria (ChU) is triggered by a sudden increase of body core temperature, e.g., induced by exercise/exertion, fever, hot baths or showers, emotional stress, hot or spicy foods, and drinks. Its prevalence is higher in young adults and peaks in winter in some patients [23, 24]. Some authors found an association with atopy and bronchial hyperresponsiveness [23, 25, 26]. A distinct sign of ChU are extensive flares of short-lived, pruritic, tiny (up to 5–6 mm) wheals, so-called pinpoint wheals. Recent studies demonstrated a lack of acetylcholinesterase in eccrine gland epithelial cells and a decreased expression of the cholinergic receptor M3 (CHRM3), probably due to an autoimmune reaction to eccrine sweat glands and/or

acetylcholine receptors, resulting in increased tissue levels of acetylcholine that stimulates mast cells degranulation [18, 27]. In addition to cholinergic agents, such as acetylcholine, histamine, allergenic components of sweat, serum factors, poral occlusion of eccrine sweat glands, and anhidrosis have been accused to induce ChU [28]. Japanese groups have suggested a ChU classification based on clinical characteristics: (1) conventional sweat allergy type, (2) follicular type with a positive ASST, (3) ChU with palpebral angioedema, and (4) ChU with acquired anhidrosis and/or hypohidrosis [27–31].

Table 1 Differential diagnosis of atypical cold urticaria (modified from [17, 18])

Atypical cold urticaria	Diagnostic criterion
Atypical acquired cold urticaria	Cold contact stimulation test negative
Delayed cold urticaria	Wheals develop up to 24 h after testing
Cold-dependent dermographism	Induced upon stroking of precooled skin
Cold-induced cholinergic urticaria	Induced by exercise in cold environment
Systemic atypical cold urticaria	Wheals plus systemic signs and symptoms upon exposure to distinct environmental cold conditions

### Vibratory Angioedema

This extremely rare variant of physical urticaria typically presents with angioedema immediately developing after exposure to local vibration [18]. Vibratory angioedema induced by snoring or dental procedures has been observed [32, 33]. Recently, a novel missense variant in ADGRE2 has been reported as the basis of autosomal dominant vibratory urticaria [34].

### Contact Urticaria

Upon contact with the provoking substance, contact urticaria immediately manifests with wheals that disappear within a few hours. The wheals are provoked by either IgE-mediated or non-immunologic mechanisms. The urticarial reaction is usually confined to the area of exposure, but may spread and cause systemic symptoms, which might be life threatening in IgE-mediated allergic contact urticaria [35, 36]. Repeated contact with the causative substance may lead to the development of dermatitis/eczema, either by non-immunological/irritant or by IgE-mediated allergic reactions. Common eliciting factors include foods, plant components (esp. sap, leaves, etc.), latex, drugs, cosmetics, industrial chemicals, animal products, or textiles [37]. Thus, contact urticaria should be recognized as an occupational skin disease, e.g., in food processing workers, healthcare professionals, and hairdressers.

### Aquagenic Urticaria

Aquagenic urticaria is a rare variant of CIndUs and shares features of both physical urticarial and contact urticaria. Patients exhibit folliculocentric wheals of 1–3 mm diameter and surrounding larger flares within 20–30 min after skin contact to water, sweat, or tears [38]. The short-lived wheals usually occur on the trunk and upper arms, while palms and soles are spared. Aquagenic urticaria has a high impact on the quality of life. Based on a recent comprehensive review, there are atypical clinical

presentations, with urticarial reactions depending on the salinity of the water, and exaggerated reactions in patients with associated systemic diseases or decreased thickness of the stratum corneum following epilation or exposure to organic solvents [38].

### Urticaria Impairs Quality of Life

In acute urticaria, pruritus had the highest negative impact on the patients’ quality of life [39]. Patients with acute urticaria were shown to be more satisfied with their lives and used emotion-focused coping and sought social support for emotional and instrumental reasons to a greater degree than patients with chronic urticaria [40]. A recent study on CU patients reported a mean total score of 36 (0–100) using the Chronic Urticaria Quality of Life Questionnaire [41]. The items with the highest mean scores were nervousness and sense of shame because of lesions [41]. In CU patients, mental health and physical impairment, activity levels on and off work as well as anxiety and depression were comparable with those of patients with moderate and severe psoriasis [42].

For the assessment of disease activity, the patients’ health-related quality of life and the disease impact on daily activities, a number of detailed questionnaires have been developed [43–45]. For daily routine, the Urticaria Activity Score (UAS) 7 is recommended which assesses the number of wheals and itch intensity on seven consecutive days (maximum score per day: six; zero = no symptoms, three =

severe symptoms) [43, 44]. The UAS7 might be amended by other disease activity parameters, e.g., the size of the largest wheal [45]. CU severity assessed by the UAS7 was shown to correlate with the impact on quality of life, sleep and daily activity interference, presence of angioedema, and diphenhydramine use [46].

## Diagnostic Procedures and Differential Diagnoses

Current guidelines of urticaria management recommend a lean diagnostic work-up that focuses on the examination of clinical signs and assessment of symptoms associated with

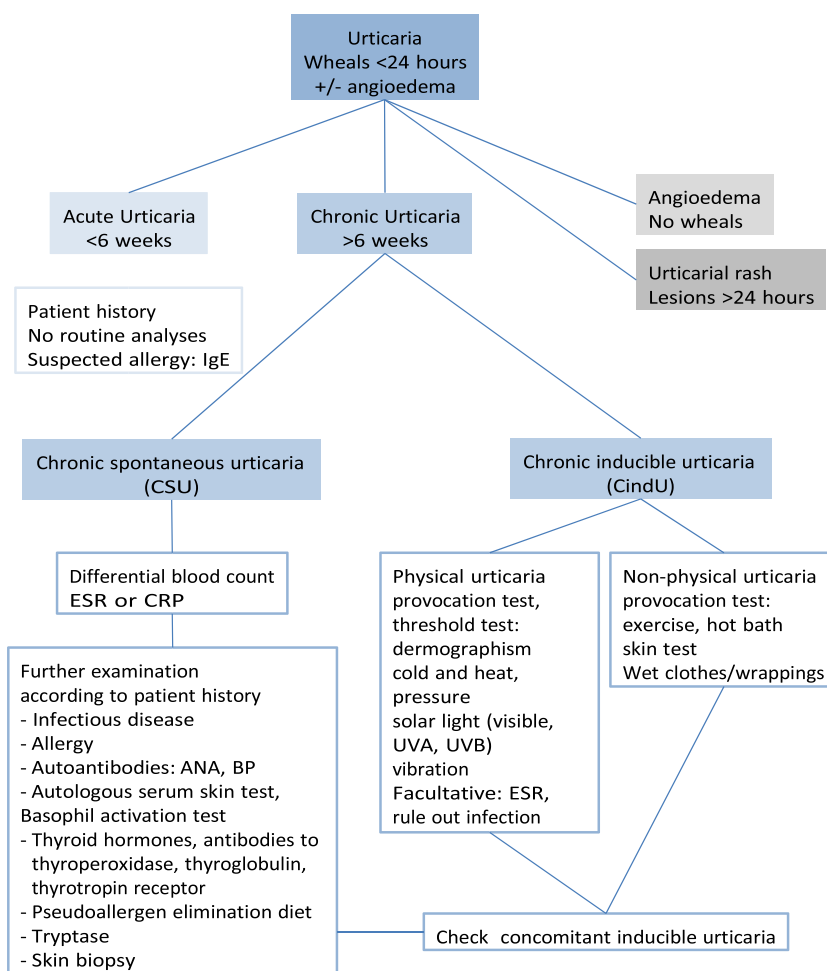
## Pathogenesis

Although urticaria is a common disease, its pathogenesis is poorly understood. Current urticaria research focuses on three topics: (1) to characterize the cells and mediators involved, (2) to identify the mechanisms of mast cell activation, and (3) to investigate (auto)immune processes associated with CSU. Here, we will provide a selection of previous published work that might be important to our understanding of urticaria and developing novel therapeutic strategies.

### Cells and Mediators Involved in Urticaria Pathogenesis

Redness, swelling, and itching of the pathognomonic

Fig. 2 Diagnostic work-up of urticaria with/without angioedema



the urticarial rash and/or angioedema (Fig. 2, Table 2).

The spectrum of differential diagnoses of acute and chronic urticarial is broad and involves hereditary and acquired diseases with urticarial rashes and/or angioedema of heterogeneous pathogenic mechanisms, summarized in Table 2. For daily practice, an algorithm guiding to differentiate urticaria with/without angioedema from bradykinin-mediated angioedema (hereditary, acquired, ACE-inhibitor induced) and interleukin-1 driven autoinflammatory diseases might be helpful [69].

wheals are the clinical correlate of vasodilatation, increased vascular permeability with leakage of fluid into the tissue, and stimulation of sensory nerve endings resulting upon activation, degranulation, and release of vasoactive substances by dermal mast cells. Mast cells contain a multitude of electro-dense granules with preformed and preactivated mediators, including effector mediators such as histamine, cytokines, and chemokines [70]. Their release precedes the generation of arachidonic acid metabolites, e.g., prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) and

leukotriene E4 (LTE4), and platelet activation factor (PAF) [71]. Among mediators synthesized by mast cell such as tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1, IL-4, IL-5, IL-6, IL-8, IL-16, CCL-2, CCL-3, and RANTES, transglutaminase (TG) 2 has been identified in the skin and peripheral blood of CSU patients [72]. These mediators

may act as chemoattractants for eosinophils, neutrophils, and T cells. Indeed, urticaria skin harbors a mixed perivascular infiltrate consistent of monocytes, eosinophils, basophils, and mainly CD4<sup>+</sup> T cells. Cytokines initiating T helper (Th) 2

Table 2 Differential diagnoses of urticaria with/without angioedema

Disease	Skin, mucosa		Other organs involved	Comments, references
	Urticarial rash	Angioedema		
Urticaria vasculitis	+		(+)	[47] Wheal >24 h, leukocytoclastic vasculitis
Normocomplementemic				
Hypocomplementemic	+		+	[48]
Autoimmune diseases				
Bullous pemphigoid	+		–	[49] Autoantibodies to bullous pemphigoid antigens BP180, BP230
Systemic lupus erythematosus (SLE)	+		+	[50, 51] Antinuclear antibodies (ANA), Increased risk of SLE in CSU (14.6)
Autoinflammatory diseases	+	(+)	+	[52–54] Interleukin 1-mediated
Cryopyrin-associated periodic syndrome (CAPS)	+			[55] Cryopyrin NLRP3 gene mutations
Familial cold autoinflammatory syndrome (FCAS)	+			Cold urticaria, fever, arthritis
Muckle-Wells syndrome (MWS)	+			Deafness, amyloidosis
Chronic infantile neurological, cutaneous and articular syndrome (CINCA)	+			Polyarthritis, chronic meningitis, fever
Schnitzler syndrome	+			[56] Monoclonal IgM gammopathy
Neutrophilic dermatoses	+		(+)	[57, 58] Peripheral blood and skin neutrophilia
Sweet syndrome	+			
Eosinophilic dermatoses				[59] Skin eosinophilia, flame figures
Eosinophilic dermatitis	+			
Wells' syndrome	+			
Infectious/parasitic diseases				
Arthropod reactions	+	(+)		
Viral exanthema	+		(+)	[60]



Drug induced			[61]
Beta-lactam-antibiotics	+	(+)	IgE mediated
NSAID	+	(+)	COX-1 inhibitors
Muscle relaxants	+	(+)	
Platin salts	+	(+)	
Taxans	+	(+)	

Table 2 (continued)

Disease	Skin, mucosa		O	Comments, references
	her organs	Urticarial involved rash	Angioedema	
Polymorphic eruption of pregnancy	+			[62]
Angioedema		+		[63, 64]
Hereditary		+	+	Complement C1-inhibitor quantity or function and C4 decreased
Acquired		+	+	Angioedema of respiratory and gastrointestinal tract
Angiotensin-converting enzyme (ACE) inhibitors		+	+	Bradykinin mediated
Angiotensin (AT) receptor blockers				
Anaphylaxis	+	+	+	[65–67]
Mastocytosis				Specific IgE [68]
				Serum tryptase, skin, and bone marrow biopsy
Cutaneous	(+)		–	
Systemic	(+)		+	

immune response such as IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) along with IL-4 and IL-5 are present in lesional skin [73]. This observation together with previous reports on the expression of INF- $\gamma$  and TNF- $\alpha$  [74] suggest a mixed Th2/Th1 immune response. Cholinergic urticaria was reported to be associated with a atopic predisposition in 57% of the patients, in whom high Erlangen atopy scores corresponding to a distinct atopic predisposition of the skin were linked to high severity and impact on quality of life [75]. Several other mediators such as vascular endothelial growth factor, matrix metalloproteinase-9, and IL-6 have been found to be elevated in the peripheral blood of CSU patients [76–78].

However, whether these phenomena are specific or part of a general inflammatory milieu needs to be investigated.

Recent research has focused on a role of basophils in urticaria. Both peripheral blood basopenia and altered basophil Fc $\epsilon$ RI function have been documented in CU patients [79]. Interval improvements of disease severity in CSU patients were associated with increased basophil numbers and IgE-mediated histamine release [80]. The reduced expression of the chemoattractant receptor-homologous molecule expressed on TH2 cells (CRTH2) on basophils and eosinophils in CSU patients compared with healthy controls has been assumed a result of an ongoing PGD2 stimulation [81]. In the sera of CSU patients, increased IL-31 levels have been detected. IL-31 is



released by basophils and may stimulate basophil chemotaxis and activate IL-4 and IL-13 release [82]. The increased expression of CD63 on basophils found in CSU patients correlated with allergic sensitization, serum autoreactivity, and basophil reactivity [83]. Interestingly, a paradoxical downregulation of FcεRI/anti-FcεRI/ anti-IgE triggered histamine release from basophils has been documented in CU patients [84]. Serum of patients with active CSU was shown to suppress basophil FcεRI activity, even when IgE and IgG were depleted [85]. Whether the alterations of basophils in urticaria are pathogenic or secondary events is currently under investigation.

In CSU patients, eosinophilia has been observed in lesional skin and may persist in non-lesional skin. This observation, together with microvascular changes and increased mast cell numbers, suggests that non-lesional skin is primed for further whealing [86]. Both major basic protein and eosinophil peroxidase may induce histamine release from human mast cells [87]. A further role of eosinophils in CU has been proposed in the activation of the coagulation system due to their tissue factor expression [88].

#### Mast Cell Activation

In up to 40% of the patients with CSU, autoantibodies directed against the α-chain of the high affinity IgE receptor (FcεRI) and/ or IgE of the complement fixing subtypes IgG1 and IgG3 have been found [89]. Autoantibodies binding to their target results in complement activation, subsequent C5a formation that binds to the C5a receptor on mast cells leading to their activation and degranulation [90]. Since a diagnostic test measuring functionally active autoantibodies has not yet been made available, the diagnosis of autoimmune urticaria (AIU) is still obscure [9]. Interestingly, chemokines such as CCL17, CCL26, and CCL27 were significantly increased in patients with AIU in comparison to other forms of CU and correlated with disease severity [91].

Insights in the intracellular signal transduction pathways might elucidate new therapeutic targets. Recently, it has been shown that upon an activation of the β- and γ-chain of the FcεRI, immunoreceptor tyrosine-based activation motifs (ITAMs) are phosphorylated, which associate with Srcfamily protein tyrosine kinases, such as Syk. The deactivation is regulated by signal regulatory proteins containing inhibitory motifs (ITIMs) that recruit SHIP 1 and 2 which dephosphorylate the ITAMs [84]. In CU, altered levels of SHIP 1 and SHIP2 have been found [92]. In patients with non-steroidal antiinflammatory drug

(NSAID)-induced urticaria/angioedema, significant associations of polymorphisms in three key genes, involved in mast cell activation including Syk, have been observed [93].

The coagulation cascade is activated in CSU and involves both the extrinsic and intrinsic pathways [94–96]. Tissue factor over-expressed by eosinophils that are activated via CD23, the low affinity IgE receptor, has been identified as a trigger [88, 97]. Sera from CU patients have been demonstrated to activate mast cell degranulation in an IgE- and IgG-independent manner and to increase vascular permeability [98]. However, the identity and function of these serum factors need yet to be identified. Interestingly, PAF may induce whealand-flare reactions independent of histamine release and mast cell degranulation [99].

#### Association of Urticaria with Autoimmunity and Infection

There is increasing evidence that autoimmunity plays a causative role in CSU [9]. Type I (IgE-autoantibodies to autoantigens, e.g., thyroperoxidase (TPO)) and type II (IgG-autoantibodies to IgE or FcεRI) autoimmunity seem to be relevant in distinct CSU subpopulations rather than the same patients. Arguments supporting this concept are (1) the identification of two distinct subgroups with either low or high titers of anti-TPO IgE-antibodies (IgEanti-TPO<sup>low</sup> and IgE-anti-TPO<sup>high</sup>), (2) the absence of a correlation between IgE-autoantibodies and ASST response, (3) the correlation of IgG- but not IgEautoantibodies with disease activity/severity, and (4) different tempi of response to omalizumab [9]. In cholinergic urticaria, a hypersensitivity to sweat substances leaking from syringeal ducts to the dermis as well as an activation of mast cells by acetylcholine that is released by nerve cells but may not bind to its receptor because of reduced expression are discussed as main pathogenic mechanisms [100].

A recent meta-analysis confirmed the association of CU with thyroid autoimmunity reporting a higher prevalence of positive thyroid autoantibodies in patients with urticaria than non-urticaria controls (OR 6.55) [101]. The presence of anti-TPO-IgE is found in up to 54% of the CU patients [102], and a recent study suggested an autoallergic mast cell activation by anti-TPO-IgE [103].

The role of *Helicobacter pylori* (Hp) in CSU has controversially been discussed. Currently, it seems obvious that the prevalence of Hp infection is not increased in CSU patients, the effect of standard CSU treatment does not depend on Hp status, and Hp eradication does not have any additional beneficial effect on CSU [104]. A recent study

showed an association with previous HHV-6 infection, persistent viral gene expression, and replication with CSU [105]. A systematic review on internal parasites revealed that CSU patients were more often diagnosed with protozoa, e.g., *Blastocystis hominis*, and had a significantly higher risk of *Toxocara* seropositivity and *Anisakis* simplex sensitization as compared to healthy controls [106].

## Therapy

### Guidelines for Urticaria Management

According to current recommendations, the aim is a complete symptom control as safe as possible [2]. All factors identified to trigger urticaria in a certain individual should be avoided. As first-line therapy, second-generation, non-sedating H1-antihistamines are used. Dose escalation up to fourfold dosage of antihistamines serves as second-line strategy. In case symptoms persist, an add-on of omalizumab, ciclosporin, or montelukast is recommended [2]. The American guidelines on urticaria management slightly differ from the European treatment standards [1]. Here, we will discuss new aspects in the management of urticaria and novel approaches. Use of Non-Sedating Antihistamines

Antihistamines act as inverse agonist of the histamine (H) 1 receptor and thus stabilize its inactive conformation [107]. Antihistamines may be up-dosed fourfold to the recommended standard dose. A questionnaire-based analysis revealed that patients who had up-dosed antihistamines reported a significant added benefit from taking two to four tablets daily while the number of reports of unwanted effects and sedation following up dosing was not significantly different from those reported for standard doses [108]. In patients with cold contact urticaria, up-dosing of bilastine resulted in a significantly better effectiveness without evidence of increased sedation with dose escalation [109]. Since sedating antihistamines added on to second generation antihistamines had no additional effects on CSU, but significantly increased daytime somnolence, they are not recommended for urticaria therapy anymore [110]. Treatment of Children with Urticaria

Analogous to the adult patients, the same first-line therapy and up-dosing of non-sedating second generation antihistamines (weight adjusted) should be applied in children (2). Preferably, substances with proven efficacy

and safety, e.g., cetirizine, desloratadine, and fexofenadine, should be used (2). Further steps have to be considered on an individual basis (2).

### Omalizumab

The anti-IgE antibody omalizumab has been proven an efficacious and a well-tolerated therapy in patients with CSU refractory to antihistamines [111]. Recent publications also show its efficacy and safety in CIndUs, even though randomized controlled trials are still lacking [112, 113]. So far, the mechanisms of action of omalizumab are not fully understood. A recent review summarized potential mechanisms that include reducing mast cell activation, reversing basopenia, and improving basophil IgE receptor function, reducing the activity of IgG autoantibodies against FcεRI and IgE, of IgE autoantibodies against an antigen or autoantigen as well as of intrinsically abnormal IgE, and decreasing coagulation abnormalities associated with disease activity [10, 79]. Omalizumab 300 mg every 4 weeks achieves fast responses and sustained effects [114] and significantly reduces the incidence of angioedema [115]. Patients with positive basophil histamine release assay and ASST tend to have a slow response to omalizumab therapy suggesting that omalizumab acts via reducing FcεRI expression [116]. An omalizumab treatment for 6 months might not be sufficient to control the disease [117]. Of note, retreatment of patients with CSU and/or CIndUs who initially responded to omalizumab, and experienced a relapse after suspending it, is considered as effective and safe as first treatment [118]. In case of a long-term therapy being required, a reduction of omalizumab dosage to 150 mg and/or extension of application interval is recommended [119].

### Ciclosporin

Ciclosporin is known to reduce the histamine release of both mast cells and basophils and affect T cell activity. Based on the evidence of several randomized controlled trials, it is recommended as a third-line therapy [2]. Because of their better efficacy, ciclosporin and omalizumab have been favored over montelukast [120]. However, the safety profile of omalizumab was superior to that of other systemic therapies for urticaria including ciclosporin [121].

Table 3 Novel approaches for the treatment of urticaria

Target	Drug name	Mechanism	Phase	ClinicalTrials.gov
IgE	Ligelizumab	Humanized monoclonal antibody targeting Cε3 domain of IgE [124]	Phase 2b	NCT02477332
	Quilizumab	Humanized monoclonal antibody targeting M1-prime segment of membrane bound IgE on IgE-switched B cells, IgE memory B cells and plasmablasts [125]	Phase 2	NCT01987947
Syk	GSK2646264	Potent and selective topical Syk inhibitor [123]	Phase 1	NCT02424799
CRTh2	AZD1981	CRTh2 antagonist [123]	Phase 2a	NCT02031679
IL-1β	Canakinumab	Human monoclonal anti-IL 1β antibody [126]	Phase 2	NCT01635127
	Rilonacept	Dimeric fusion protein composed of ligand binding domain of IL-1 receptor and IL-1R accessory protein bound to IgG1 [126]	Phase 2	NCT02171416
Vitamin D3		Supplementation because of reduced vitamin D levels in CU patients [127]	Phase 3	NCT02873364

#### Inhibition of Tumor Necrosis Factor-α

Increased levels of TNF-α in skin samples of CU are the rational for the use of anti-TNF-α therapy in histamineresistant CU. A single center retrospective observational study reported that upon therapy with TNF-α inhibitors, a total of 15 of 25 (60%) patients with refractory CU achieved a complete or almost complete resolution of symptoms [122].

#### Novel Therapeutic Approaches

Recent research has improved our understanding of the pathogenesis of urticaria, in particular about the cells and mediators involved, signaling pathways, triggers, and associated autoimmune and infectious phenomena. Thus, a broad spectrum of potential therapeutic targets has been identified. The most promising recent strategies have been summarized [123]:

- The development of more efficient antibodies targeting IgE and IgE receptor
- Blocking the recruitment and activation of inflammatory cells
- Inhibiting mast cell activation by blocking signaling pathways
- Blocking pro-inflammatory cytokines and neuropeptides
- Targeting complement C5a and C5a receptor
- Supplementing vitamin D

Currently registered clinical trials for urticaria therapy are given in Table 3.

#### Outlook

As this review demonstrates, immense progress has been made in understanding the pathogenesis and management of urticaria over the last decade. The launch of omalizumab has not only fundamentally improved urticaria treatment, it has also stimulated research in the field. So far, the causes and mechanisms of mast cell activation in urticaria patients have not completely been understood. Expanding our knowledge on urticaria pathogenesis, its genetics and phenotypes will have a direct impact on clinical praxis toward a personalized medicine and the development of novel therapies.

#### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Funding** None.

**Research Involving Human Participants and/or Animals** Not applicable.

**Ethical Approval and Informed Consent** Not applicable.

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